C-reactive Protein of Clinical Outcomes in COVID-19 Basra Patients

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Abstract

   By the time we conducted the current study,- COVID-19 epidemic has already become a global challenge, paralyzing socio-economic activity dramatically. Hence   **,** this study aimed to identify the most valuable prognostic indicators for COVID19 patients' early and accurate diagnosis by comparing laboratory biomarkers like C -reactive protein between non-severe and severe groups of patients**.** Depending on clinical symptoms, ---337 COVID-19 patients were enrolled at the Basra City Hospital from March 29 to April 29,2020   were classified into severe and non severe groups.

   A total of 337 patients were diagnosed with COVID-19, including 306 (128 males and 178 females) were adult patients, and ---31 (10 male and 21 female) Child & teens patients. The mean age of the adult patients was 42.79 ± 16.22 (age rnage 18-85 years),----- Child & teens patients was 12.23 ± 4.06. All children and more adults had an initial normal C-reactive protein (CRP) <5 mg/L.

   CRP in severe group (68.51 ± 66.38) was assigned to 27 adult patients (8.82%), and the differences were high significantly ($p < 0.05$) compared to the non severe group (24.31 ± 45.26). There were significant differences ($p < 0.05$) between the severe group and non- severe groups in all parameters, including hemoglobin, platelet count, white blood cells (WBCs) count, CRP, ferritin as well as erythrocyte sedimentation rate ″ESR″.
 ---The results of this study indicated,--- that in the majority of children ----with COVID-19 infection , threre was no increase in CRP levels and other biomarkers.On the other hand, a positive link was found between COVID-19 severity and CRP, ESR, and ferritin levels in adults.

 Keywords: COVID-19, CRP,WBC$_S$,and   ESR

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بروتين سي التفاعلي والعديد من الموشرات البيوكيميائية لمرضى كوفيد –19في البصرة

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الخلاصة

لقد اصبح COVID-19 وباءا و تحديا عالميا وشل النشاط الاجتماعي والاقتصادي بشكل كبيروقت اجراء هذا البحث. لذا هدفت هذه الدراسة إلى تحديد المؤشرات الأكثر قيمة للتشخيص المبكر والدقيق لمرضى COVID19 من خلال مقارنة المؤشرات الحيوية المختبرية مثل البروتين سي التفاعلي CRP بين مجموعتين من المرضى ذوي الاعراض الحادة وغيرالحادة. تم تسجيل 337 مريضا من مرضى COVID-19 في مستشفى البصرة التعليمي للفتره من 29مارس الى 29ابريل لعام 2020 تم تصنيف المرضى الى مجموعتين اعتمادا على الاعراض السريرية احدهما حادة والاخرى غير حادة.كان عدد البالغين 306 مريضا (128اذكرا و178 من الاناث) بالاضافة الى 31 من الاطفال والمراهقين (10اذكور و21 من الاناث) كان متوسط عمر المرضى البالغين 42.79±16.22 سنة (المدى بين 18–85 سنة) وكان متوسط عمر الاطفال والمراهقين 4.06 ± 12.23. كان مستوى بروتين سي التفاعلي في جميع الاطفال والمراهقين ضمن المستوى الطبيعي أي اقل من 5 ملجم /لتر.

لوحظ ان مستوى بروتين سي التفاعلي في مجموعة المرضى ذوي الاعراض الحادة هو 68.51±66.38 مجم/لتر والبالغ عددهم 27 مريضا أي بنسبة (8.8%) وكانت الفروقات عالية المعنوية 0.05> p عند مقارنتها بالمجموعة ذات الاعراض غير الحادة 45.26 ±24.31مجم/لتر , وكذلك لوحظ وجود فروقات عالية المعنوية بين المجموعتين في جميع المتغيرات وقد شملت الهيموغلوبين ، عدد الصفائح الدموية ،وعدد خلايا الدم البيضاء ، مستوى الفيريتيين وكذلك معدل ترسيب كريات الدم الحمراء .

في الختام، هذه الدراسة بينت ان غالبية الإصابات بفيروس COVID-19 لدى الأطفال لم تسبب زيادة في مستويات بروتين سي التفاعلي CRP وغيره من المؤشرات الحيوية. على الرغم من ذلك ، وجدت هذه الدراسة علاقة إيجابية بين شدة COVID-19 ومستويات CRP ،ومعدل ترسيب كريات الدم الحمراء والفيريتين لدى البالغين.

Introduction

The COVID-19 epidemic has already become a global challenge, paralyzing socio-economic activity dramatically. The diagnosis of COVID-19 patients was focused mostly on the discovery of laboratory biomarkers as they coud accurately predict severity of disease[1]. Depending on the risk and in order to ensure prompt therapy, it became critical to establish acceptable biomarkers able of classifying patients [2].

The inflammation in Coronavirus-2 ″SARS-CoV-2 ″ is a characteristic of the 2019 coronavirus illness (COVID-19), and most of hospitalized patients with COVID-19 exhibited elevated inflammatory biomarkers [3]. CRP is a biomarker of inflammatory response that is released by --liver and was first reported by Tillett and Francis [4]. According to certain research, CRP levels can be diagnosed in the early stage of pneumonia, and greater CRP levels are related with severe pneumonia [5]. Several of recent series have observed a link between increasing CRP levels and worsening severity of disease in COVID-19[6-9]. Though changes in WBC, and ESR in COVID19 patients have previously been described, still little is known regarding their relationship with disease severity [10, 11]. As a result, laboratory biomarkers could possibly be allowed to identify the early inflammatory and severe cases.

As compared to younger adults, adolescents and children with the elderly--ِ preliminary data showed that the elderly, particularly those with known underlying health issues, awere disproportionally at risk for severe COVID-19-related illness and death [10,12, 13]. Among the most striking and constant results from COVID-19 studies around the world is that, unlike infected adults, children rarely developed severe illnesses.

Hence, in order to find the most valuable prognostic indicators for COVID19 patients' early and accurate assessment, this study analyzed CRP and other hematological biomarkers between non -severe and severe COVID19 patients---.

Materials and Methods
Study Design, and Participants
This retrospective study was carried out at Basra Teaching Hospital, that was designated to treat COVID-19 patients. Between March 29 and April 29, 2020, the hospital confirmed 337 cases including 306 (128 males and 178 females) adult patients, and 31 (10 males and 21 females) child & teens patients, ranging in age from 1 to 85 years. All patients with confirmed COVID-19 infection (positive nasopharyngeal/throat swab specimens by reverse transcription-polymerase chain reaction (RT-PCR)), --- according to the WHO interim guidance,--- were included. Whereas suspected cases (negative nasopharyngeal/throat swab specimens by RT-PCR) with similar clinical symptoms were excluded.

Data Collection
Manual perusals of inpatients case sheets were used to review patient medical records. Using a data collecting checklist, data on epidemiological, clinical, laboratory, and outcome measures was gathered from electronic medical records---. In addition, patients information such as demographics, past medical history (PMH), underlying medical conditions, symptoms, and indicators, as well as preliminary laboratory tests
such as CRP, ESR, and the detection of serum ferritin, WBCs, and platelet count, was also collected.

Statistical Analysis
Statistical Package for Social Sciences (SPSS) version 19 (IBM; Chicago; IL; USA) was used to analyze the data. The median, number and percentage were used to represent continuous and categorical data respectively.--- Student's t-test was utilized to compare continuous and categorical variables.

Results
A total of 337 COVID -19 patients with 128 males and 178 females among the adult patients and 10 males and 21 females among the child and teen patients, were included in this investigation,-- Table 1 shows that the average age of the adult patients was 42.79 ±16.22 (ranging between 18-85 years). Male patients had a mean age of 43.52 ±6.15 (ranging between 18-84 years), whereas female patients had a mean age of 42.27 ±16.29 (ranging between 18-85 years). The mean age of the children and adolescent patients was 12.23 ±3.06, with a male mean age of 9.10 ±4.81 in the range 3-17 years and female mean age of 13.19 ±3.73 in the range 1–17 years.

Table 1: Number and average age of children and teens and adult COVID-19 patients

Patients	Overall	Male	Female
No.of Child&Teens Patients	31	10	21
No.of Adult Patients	306	128	178
Average Age of Child &Teens	12.23	9.10	13.19
Average Age of Adults	42.79	43.52	42.27

Non-severe instances (asymptomatic, mild, and moderate) were found in 310 (91.99%) of all patients, including 279 adults and all children and teenagers. While, 27 adult patients (severe and critical) were assigned to the severe group (8.01 percent) as shown in Table 2.

Table 2: Number and percentage of adult and children COVID-19 patients dependent on severe and non severe groups

Patients	Non-severe Group				Severe Group		
	Asymptomatic	Mild	Moderate	Sum of Non-Severe Group	Severe	Critical	Sum of Severe Group
Adults, Child & Teens Patients	119(35.31%)	133(39.47%)	58(17.21%)	310(91.99%)	23(6.82%)	4(1.18%)	27(8.01%)
Adults Patients	103(33.66%)	121(39.54%)	55(17.98%)	279(91.18%)	23(6.82%)	4(1.18%)	27(8.01%)
Child & Teens Patients	16(51.61%)	12(38.71%)	3(9.68%)	31(100.00%)	0(0.00%)	0(0.00%)	0(0.00%)

Only 147 of 306 adult patients (48.03%) and 27 of 31 children and adolescent patients (87.09%) had an initial CRP of less than 5 mg/L. The severe group's mean CRP was 68.51±66.38, which was significantly higher (p<0.05) than the non-severe group (24.32±45.26).

Table 3 shows the laboratory findings of adult individuals with COVID-19 patients. Both in the severe and non-server groups, only platelet counts were within normal limits. --However, hemoglobin levels were low in the severe group as compared to the reference range and the non-severe group, there were no statistical- differences (p>0.05) between the severe and non-severe groups.There were significant variations in means of CRP, WBC count, ferritin, and ESR levels (p<0.000) between the severe and non-severe groups

Table 3: Levels of the inflammatory markers in COVID-19 adult patients (Mean ± SD)

Patients	References Range	Non-Severe Group	Severe Group	P-value
CRP	0-5 mg/L	24.32±45.26	68.51±66.38	0.000
Hb	12-15gm/dL	12.37±2.00	10.97±1.96	0.735
Platelet Count	150-450*10^9/L	285.63±99.35	298.5±119.97	0.003
WBC	4.00-10.00*10^9/L	7.74±3.16	10.54±6.85	0.000
Ferritin	13-150 ng/ml	132.96±136.15	272.53±307.12	0.000
ESR	0-20 mm/hr	35.84±56.55	81.08±33.76	0.000

Clinical tests revealed that no severe cases were present in all child and adolescent patients (Table 4). Hb, platelets, WBC, CRP, ferritin, and ESR values were all within normal limits

Table 4: Levels of the inflammatory markers (Mean ± SD) in COVID-19 child patients

Patients	References Range	Non-Severe Group
CRP	0-5 mg/L	3.73±5.41
Hb	11-13gm/dL	11.80±1.17

Platelet	150-400*10^9/L	355.23*10^9 ± 187.12
WBC	4.00-26.00*10^9/L	8.29*10^9 ± 2.94
Ferritin	13-150 ng/ml	62.33±144.2
ESR	0-20 mm/hr	10.33±13.80

WBC, platelet count, ferritin and ESR were all linked to elevated CRP values at the presentation (Figure 1). The association between CRP levels and WBC, platelet counts, ferritin and ESR was found to be positive where the R values were 0.208, 0.048, 0.301 and 0.320 respectively.
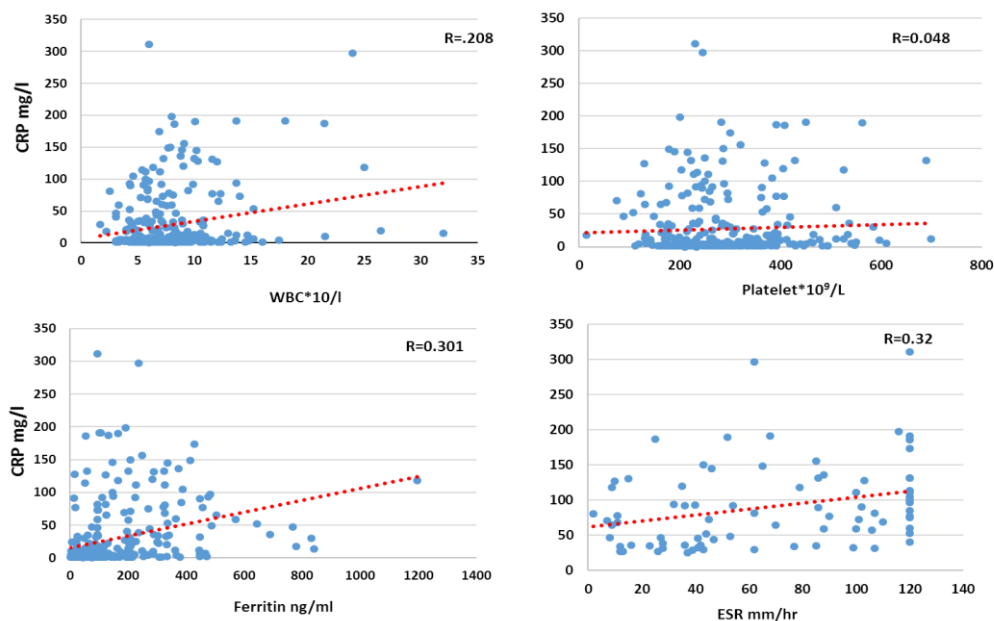

Figure 1: WBC, platelet count, ferritin and ESR levels are positively correlated with CRP levels

The correlation between CRP levels and disease severity was found to be positive with 0.385 R value as shown in Figure 2.
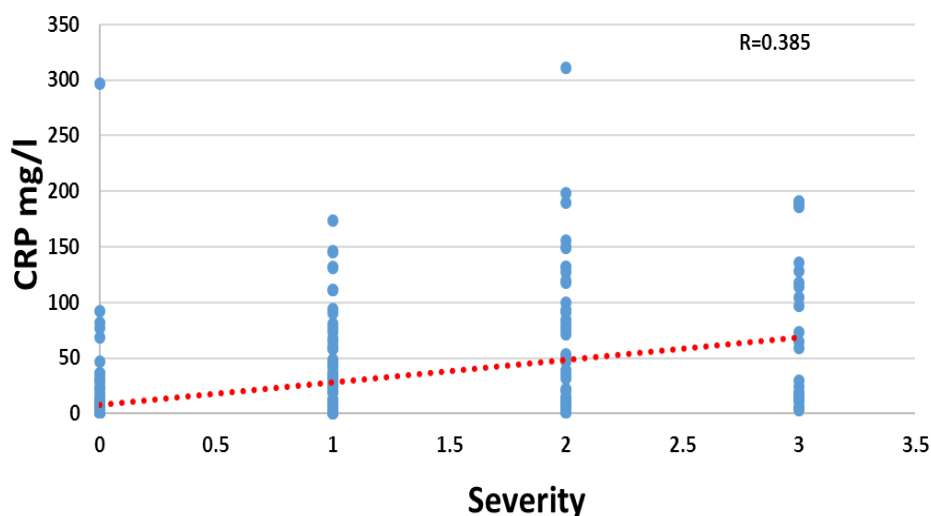

Figure 2 : The correlation among the levels of CRP and the severity of disease Cases that are non- severe (Asymptomatic= 0 , Mild= 1, Moderate= 2) and cases that are severe (Severe=3)

Discussion

Severe COVID-19 is the hyper inflammatory response arising from the SARS-CoV-2-induced activation of both innate and cellular immunity which is described as an uncontrolled. inflammation in disease by-- producing of high levels of proinflammatory cytokines such as ″TNF-α, IL-1 and IL-6″, CRP, ESR and ferritin--. The clinical features of severe and non-severe COVID-19 patients were compared in this study, and possible factors related to disease progression and severities were investigated. CRP levels are one of the inflammatory biomarkers that rise considerably during early period of disease and there is a positive relationship between higher CRP levels and severity of the disease [14, 15] (Figure 2) . Tan et al.[16] found that at 20.42 mg/L CRP shows good diagnostics in the early period of severe COVID-19. According to the research CRP levels may reflect disease severity in the beginning stages of COVID-19 [17]. CRP is a highly sensitive biomarker of the acute phase as an inflammatory response, infection, as well as tissue damage [18]. Hence, and it can be utilized as an inflammation indicator [19].

In the current investigation, CRP levels in adults were found to be considerably greater significantly (p< 0.05) in severe instances (68.51±66.38, Table 3) than in non-severe cases,thus suggesting that CRP could possibly be a biomarker in COVID-19 severity and its progression in patients---. Our findings agree with those of [20,21], who found that COVID-19-severe cases--- had significantly higher CRP levels than non-severe patients, suggesting that this biomarker can be used to assess disease development. This was corroborated by a meta-analysis conducted by Fasa to investigate of--- CRP levels as a potential biomarker of this disease [22].

ESR is a non- specific inflammatory metric that mostly represents changes in the types of plasma protein[23]. ESR levels were also observed to be --significantly higher (p< 0.05) in the adults severe group (81.08±33.76 mm/hr) than in the non-severe group (35.8456.55 mm/hr) (Table 3).

According to Zeng *et al*.--[19] who conducted a meta-analysis study, the severe group had -higher ESR level than the non-severe group. One reason is that the severe group's patients experienced more inflammation. Another possibility is that individuals in the severe group with older ages- contributed to the - higher - ESR level as its level increased with age [24].
Serum ferritin levels in the severe group (272.53±307.12 ng/l) were found to be considerably ahigher (p <0.000), as were other indicators in this investigation (Table 3). Ferritin is a biomarker of stored iron that rises in serum during viral infections and can also serve as a marker for virus replication [25, 26]. According to Zhou *et al.*-- [27]- an increase in ferritin level is linked to a deterioration of COVID-19. Similarly, Shekhanawar *et al.* -- discovered that individuals with severe respiratory distress had greater ferritin levels than those with less severe respiratory distress [26].

Excessive inflammatory response is linked to the severity of COVID-19 [28]. There is a considerable increase in inflammatory cytokines and biomarkers such as interleukin-2, CRP, ferritin in the systemic inflammation phase of COVID-19, as described by Siddiqi and Mehra -[29]. They confirmed that this stage includes the cytokine storm's most severe expression, in which extreme hyperinflammation can lead to cardiopulmonary collapse and multi-organ failure. Finally, our findings revealed that serum CRP, ESR- and ferritin levels were significantly higher in severe COVID-19 instances compared to non-severe cases, and that they can serve as major predictors of disease severity at the time of admission [26, 30, 19]. Patients with mild–moderate COVID-19- infection, on the other hand, have normal levels of CRP, ESR and serum ferritin. Whereas severe infections have elevated levels of these inflammatory

responses. Children and teens, unlike sick adults, do not develop severe manifestations of the disease. Finally, in the COVID-19-inflammatory indicators, particularly CRP with WBC, platelet counts, ferritin and ESR (Figure 1), -have been found to be strongly correlated. The R values were 0.164, 0.061, 0.403- and 0.290- respectively.

-According to a certain research, thrombocytopenia has been connected to the severity of disease and is associated with mortality of patients. It has been found that as platelet count drops, mortality rises [31, 32]. In another investigation, platelet levels were observed to be within in normal range in many COVID-19 patients at the time of hospital admission [33], which is comparable to our findings. The time of the test could be a factor in the discrepancies between studies. Platelets are involved in inflammatory signals as well as the immune response to infections [34] and - may assist in target hemostasis and immunological responses against possible infection to avoid invasion of microbes by combining thrombotic and immune recruiting roles [35]. Platelets can interact with many viruses directly through a number of receptors, -like Toll-like receptors [36]. Platelets can absorb and agglomerate pathogens [37]. Depending on the infection, platelets and their products can decrease viral infection [38]. Platelets appear to play an important role in white blood cell diapedesis by attracting and stimulating circulating leukocytes to the endothelium surface [35, 39]. In the procoagulant effect of viral infections, interactions between endothelial cells, platelets- and leukocytes are crucial [38]. In viral infections, thrombocytopenia, platelets release-and interactions with leukocytes may have either harmful or beneficial immunological effects [34]. Finally, platelet count testing is a common aspect of laboratory examinations, and researchers have observed dthe test of platelet count providing additional information about the patient's condition [40].

Conclusion
COVID-19 is an adult-onset disease with a variety of symptoms. The majority of infections with COVID-19 in children - just have minor clinical signs and don't cause an increase in the-CRP levels and other biomarkers.- On the contrary, -severity of COVID-19 in adults has been found to be positively linked with CRP, ESR-and ferritin levels in this study.

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